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Chapter 6

Posttreatment assessment of women at risk of developing high-grade cervical disease: Proposal for new guidelines based on data from The Netherlands

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Abstract

Objective Women treated for high-grade cervical disease (cervical intraepithelial neoplasia grade 2 or grade 3 (CIN2/3)) face a significant risk of developing post-treatment disease. Therefore, in most European countries, they are monitored by cytologic testing at 6, 12, and 24 months after treatment. Although testing for high-risk types of the human papillomavirus (hrHPV) in the follow-up seems to be a valuable supplementary method, its use is not yet fully explored.

Methods Besides reviewing the literature, we completed a long-term follow-up study describing the cumulative risk for CIN2/3 or cancer (CIN2+) of different hrHPV and cytology test results after treatment.

Conclusions High-risk HPV testing improves the sensitivity to detect posttreatment CIN2/3 (relative sensitivity = 1.15, 95% confidence interval (CI) = 1.06-1.25), but the highest sensitivity (95%, 95%CI = 91%-98%) is reached by performing cotesting (both cytology and hrHPV). The CIN2+ risk after a single negative cotesting result taken 6 months after treatments was similar to the risk after 3 consecutive negative cytologic test results (5-y CIN2+ risk being 3.0% (95%CI =1.5%-6.1%) and 2.9% (95%CI = 1.2%-7.1%), respectively). Women who test negative for cotesting at both 6 and 24 months after treatment have a minimal risk of developing CIN3+ in the next 5 years (0.0%, 95%CI = 0.0%-3.0%).

Recommendations We propose a new posttreatment surveillance protocol, consisting of combined testing with both cytology and hrHPV at 6 and 24 months after treatment. After 2 negative cotesting results, women should be retested after 5 years.

Rationale

In the Netherlands, approximately 6.000 women¹ with high-grade cervical disease (cervical intraepithelial neoplasia grade 2 and grade 3 (CIN2/3)) are detected annually. By excision of the transformation zone, progression to cervical cancer is prevented. Because 10 to 15% of these women are subsequently diagnosed with residual or recurrent (posttreatment) CIN2/3²⁻³, it is imperative to identify women with posttreatment disease, thereby having the possibility to repeat conservative treatment and to reduce the risk for future invasive disease. The aim of posttreatment surveillance should primarily be to identify all women with residual disease from unsuccessful treatment and women with a persistent infection with a high-risk type of the human papillomavirus (hrHPV) who have an increased risk of incident lesions.⁴

Current surveillance protocol after treatment for CIN2/3

Presently, 10 to 15% of women treated for CIN2/3 present with posttreatment disease.²⁻³ In most European countries, treated women are followed-up by cervical cytology taken 6, 12 and 24 months after treatment. After 3 consecutive negative test results, women return to the population-based screening program in which screening takes place at intervals of a maximum of 5 years.⁵ In other countries women receive more intensive follow-up, without better results in terms of detecting posttreatment disease.⁶⁻⁷

The current protocol has several drawbacks, namely, the low compliance rate and the limited sensitivity of cytologic screening. With regard to the compliance rate, only half of all treated women complete the entire follow-up schedule of 3 cytologic smears in the first 2 years after treatment.⁸⁻⁹ The women who withdraw from follow-up visits face an increased risk of nondetected posttreatment disease. The second problem is that women monitored after treatment may have a false-negative cytologic test result despite the presence of clinically meaningful disease.

A study¹⁰ demonstrated that the cervical cancer risk in treated women with 3 consecutive negative cytologic test results, was 4.2 times higher than the risk of women with a normal cytologic test result in population-based screening who have not been treated previously. This increased risk is mainly based on a high number of missed lesions by cytology in the first 2 years after treatment.

By improving the sensitivity of the test used, for instance by implementing hrHPV testing, this number could be reduced. As our group has demonstrated, the 5-year risk of CIN2+ (CIN grade 2, grade 3, or cancer) lesions after 3 consecutive negative test results was similar to the risk of women with both a negative hrHPV test and normal cytologic test

result taken after 6 months.³ Conversely, one could argue that although the hazard ratio is more than 4 times higher for treated women than for women with normal cytologic test results in population-based screening, their absolute risk to develop cervical cancer remains low (e.g. a 10-year risk of 0.3% in treated women versus 0.07% in women with normal cytologic test result in population-based screening). Therefore, according to the current Dutch guidelines, we consider it acceptable to refer women treated for CIN2/3 lesions back to regular screening after 3 consecutive negative smears taken 6, 12 and 24 months after treatment.

Improving the posttreatment surveillance protocol by implementing hrHPV testing

The current Dutch guidelines⁵ may be improved by increasing the sensitivity of the test and thereby the negative predictive value. This may be accomplished by implementing a test to detect the presence of hrHPV. Several studies have shown that hrHPV-testing is more sensitive than cytology for detecting posttreatment disease.¹¹⁻¹² Implementing hrHPV testing in posttreatment surveillance seems a logical choice for several reasons. First, several European countries have already implemented hrHPV-testing in post-treatment surveillance as a test of cure.^{3, 13} For instance, a pilot study with adapted guidelines is currently under evaluation in the United Kingdom.¹⁴ In these adapted guidelines treated women with normal cytology test results or with only minor abnormalities (borderline or mild dyskaryosis (BMD)) are tested with an additional hrHPV test. If negative, women are referred to the 3-yearly population-based screening program, whereas women testing hrHPV positive, or have cytology results of moderate or severe dyskaryosis (>BMD), are referred for colposcopic examination. In Denmark, treated women with free resection margins and a negative test for both cytology and hrHPV at 6 months after treatment, are referred to population-based screening (either 3- or 5-yearly depending on age).¹⁵

Second, the Health Council of the Netherlands recently advised to use hrHPV-testing as primary screening tool in the population-based screening program.¹⁶ Currently, this program consists of 5-yearly cytologic tests for all women between 30 and 60 years of age in which women with a normal cytologic test result return for screening in the next round.⁵ Their risk of developing interval CIN3+ 0.5%-0.8%,¹⁷ and considered acceptable to the general population, the health authorities, and the professionals. This risk could therefore be used as a threshold to refer women with other test results, or different testing methods, to population-based screening.^{2, 8, 19-25}

Third, the long-term cumulative risks of posttreatment CIN2+ and several different follow-up algorithms based on hrHPV and cytology test results have recently been pub-

lished to identify women at risk of developing posttreatment disease.³ These results are summarized in Table 6.1. The posttreatment CIN2+ risk was 2.9% (95%CI 1.2%-7.1%) in the next 5 years for women with 3 negative cytologic test results.³ Although higher than the CIN2+ risk in the general population, the 0.7% (95%CI 0.0%-3.9%) 5-year risk of developing CIN3+ was similar to the risk of women with normal cytologic test results in population-based screening.¹⁷ This study confirmed that most posttreatment CIN2/3 occurs within the first 2 years after treatment^{23, 26, 27}, and also that the CIN2+-risk remains increased for a longer period.²⁸⁻³⁰ . Another recently published long-term follow-up study also concludes that 2 negative cotest results gives enough reassurance against posttreatment CIN2+. In this large study the 5-year CIN2+ risk was with 1.5% (95%CI 0.3%- 7.2%) similar to the 1.0% risk (0.2%-4.6%) in Kocken et al.^{3, 31}

Table 6.1 5-years CIN2+ and CIN3+ risks after post-treatment testing³

		CIN2+ (95%CI)	CIN3+ (95%CI)
A	6-months only		
	Cytology (negative, PAP1)	5.8 (3.6-9.3)	2.2 (0.9-4.8)
	hrHPV (negative)	4.4 (2.5-7.5)	1.3 (0.5-3.5)
	Cotesting (negative)	3.0 (1.4-6.1)	1.1 (0.3-3.4)
	PAP1, hrHPV positive	27.5 (15.2-44.4)	11.2 (3.9-28.2)
B	Current follow-up		
	Cytology negative 6, 12 and 24 months	2.9 (1.2-7.0)	0.7 (0.1-3.9)
C	Both 6 and 24 months		
	hrHPV (both negative)	2.3 (1.0-5.2)	0.4 (0.0-2.5)
	Cotesting (both negative)	1.0 (0.2-4.6)	0.0 (0.0-2.9)

CIN= Cervical Intraepithelial Neoplasia; 95%CI= 95% confidence interval;

hrHPV= high-risk type of the human papilloma virus; cotesting= combined testing with hrHPV and cytology.

Table shows the 5-year risks to develop CIN2+ (consisting of CIN 2, CIN 3 and invasive cancer) and CIN3+ (including CIN3 and invasive cancer) after treatment.

In part A of the table the risks after 1-time testing at 6 months after treatment with either cytology, hrHPV or both (cotesting) are presented, just as the risk of women who have normal cytology, but are hrHPV positive (PAP1, hrHPV positive).

In part B, the current follow-up protocol is presented, with the risks after 3 consecutive negative cytologic test results (PAP1).

In part C, the alternative schedules of using sole hrHPV testing at 6 and 24 months after treatment, as well as cotesting at the same time points is presented. The latter is the protocol suggested to replace the current cytology-based practice.

Proposals for new posttreatment surveillance protocol

Several approaches for posttreatment surveillance could be considered. Here we describe the benefits and drawbacks of the following protocols: 1-time sole hrHPV testing, 1-time cotesting (consisting of combined testing with hrHPV and cytology) and 2-times cotesting (at 6 and 24 months after treatment).

Sole hrHPV testing at 6 months after treatment

As a consequence of the high sensitivity of an hrHPV test, a single positive hrHPV test result ensures the early and accurate detection of women with an increased risk for progression to, and development of, posttreatment disease. Most women clear their hrHPV infection within 6 months^{18, 32} and those testing negative are at low risk of developing posttreatment CIN2/3. Therefore, these latter women may return to the population-based screening program.^{18, 33, 34} However, sole hrHPV testing still has a few false-negative test results (pooled sensitivity of 92-93%).¹¹⁻¹² Also, these women have a CIN3+-risk of 1,3% (95%CI: 0.5%-3.5%) in the next 5 years (see Table 6.1). It can be concluded that 1-time testing with hrHPV is not sufficient to identify women with post-treatment disease. In a diagnostic setting, it is therefore preferable to use co-testing.

Arguments for co-testing after treatment

The combination of hrHPV and cytology testing has shown to have the highest sensitivity to detect posttreatment disease.^{18, 22, 25, 35}

Kocken *et al.*³ confirmed the value of hrHPV testing in posttreatment surveillance. The CIN2+-risk after 3 consecutive negative cytologic tests was with 2.9% (95% CI 1.2%-7.0%) similar to the risk after 1 negative cotesting result at 6 months after treatment (3.0%, 95%CI 1.5%-6.1%). This indicates that follow-up could be limited to only 1 test moment 6 months after treatment. Several other studies have also demonstrated that women who test negative for cotesting 6 months after treatment could omit the 12-month visit during follow-up.^{8, 18, 22, 25} In addition, cotesting these women again at 24 months reduces the CIN2+ risk further to 1.0% (0.2%-4.6%) in the next 5 years (see Table 6.1). Therefore, we argue for cotesting at both 6 and 24 months after treatment. The new surveillance protocol we propose is as follows; all women should be tested with cotesting at 6 months after treatment. Women who test positive for either test at this testing moment should be referred for colposcopy (with mandatory biopsy). For instance, women with normal cytologic test results but a positive hrHPV test at 6 months have a risk of 27.5% (95%CI 15.2%-44.4%) to develop a CIN2+ lesion within the next 5 years (see Table 6.1). Their risk is such that conservative management is not justifiable. We believe this risk can be strongly reduced by introducing colposcopy with biopsies taken from areas suspected for high-grade CIN and if no abnormalities are seen, 1 randomly taken biopsy. Our assumption is based on several studies in which is demonstrated that taking multiple biopsies from any suspicious lesion and at random taken biopsies increase the detection of high-grade lesions.³⁶⁻³⁸

Women who are diagnosed with high-grade diseases are treated, while those with no or low-grade disease (\leq CIN1) should be retested by cotesting 12 months after the initial treatment. Again, a colposcopic examination is required for women with an abnormal test result. Women with no or low-grade disease, and those with negative cotesting at 12 months, are retested 24 months after initial treatment. So, independent of previous test results, all women are retested by cotesting at 24 months after treatment to avoid missing cervical carcinoma because of test failure. Only women who test negative for both tests at 6 and 24 months may be referred to population-based screening or be re-screened after 5 years because their risk of developing CIN2+ in the next 5 years is acceptable.³ Women with 1 or both tests positive at 24 months after treatment should follow the diagnostic cycle as summarized in Figure 6.1. We rate our recommendation as AII, according to the internationally used GRADE guideline, used to indicate the strength of our recommendation and the quality of the evidence.³⁹⁻⁴⁰

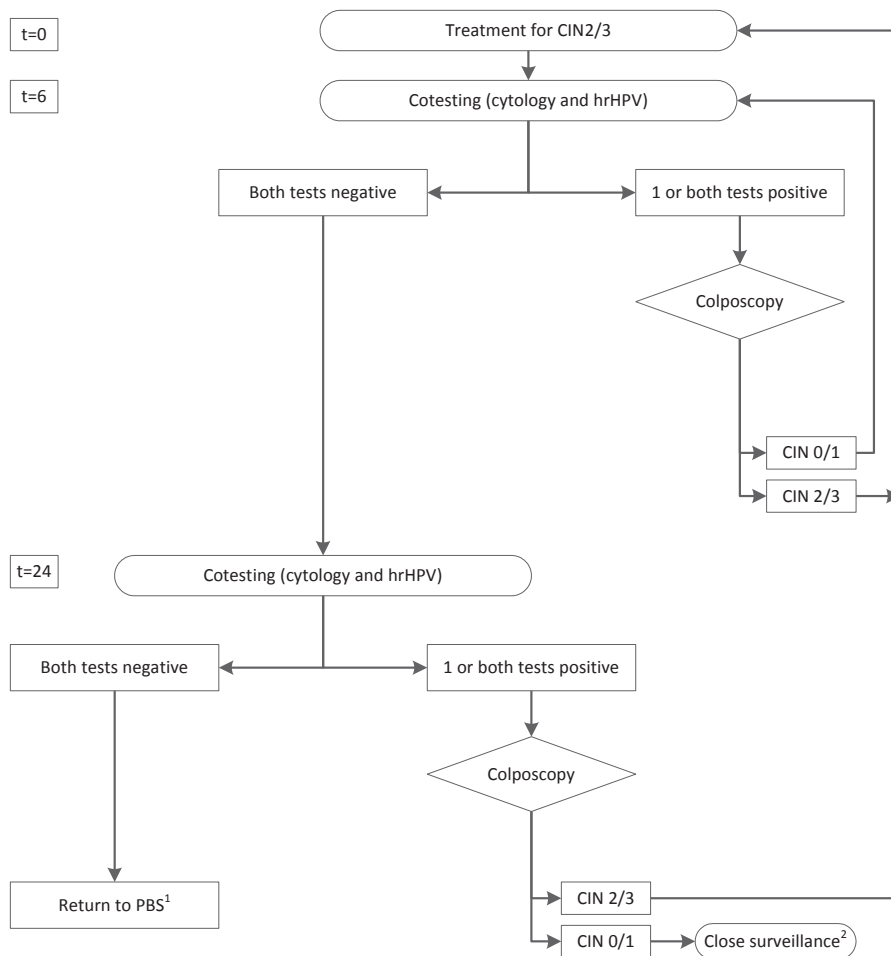
Coupé et al.⁴¹ have performed cost-effectiveness analyses for different follow-up strategies including hrHPV testing. Cotesting at both 6 and 24 months is slightly more costly than the current algorithm but is currently considered as the most safe option, as it detects the most cases of high-grade posttreatment CIN.^{8, 41}

Although CIN2 remains the consensus threshold for treatment, there are some special circumstances.

For instance, women who persistently present with cytology results of moderate or severe dyskaryosis, or positive hrHPV test results, but have only low-grade disease at colposcopy, treatment should be considered. Likewise, not every CIN2 lesion needs to be treated; for instance in young women who desire fertility, a small, easily accessible CIN2 lesion observation using cotesting with or without colposcopy at 6-month intervals could be acceptable.

It is important to keep in mind that the currently proposed adjustments only apply to women treated for CIN2/3 and does not apply to women treated for adenocarcinoma in situ (AIS). These women are currently followed up with cytology for 5 consecutive years because of the endocervical location and increased risk of multifocality. However, more evidence is gathered which suggests that a hrHPV-positive test result at any time point during follow-up is the most significant independent predictor of progressive disease in women treated for AIS.⁴² Therefore, they might also benefit if hrHPV testing is included in posttreatment surveillance.

Figure 6.1 Proposed follow-up schedule for women treated for high-grade CIN



1 Return to population-based screening or screening after 5 years.

2 Close surveillance consisting of a) cytology after 6, 12, and 24 months; referral to population-based screening program or cotesting once every 5 years when all 3 tests are negative; b) cotesting (both cytology and hrHPV) after 6 and 24 months (referral to population-based screening program or co-testing once every 5 years when both tests are negative at both time points).

In this figure, we graphically present the proposed algorithm to perform surveillance in women treated for CIN2/3. At 6 months after treatment all women will be cotested with both cytology and hrHPV. Women with an abnormal cytologic test result (BMD or worse) or with a positive hrHPV test will be referred for colposcopic examination with mandatory biopsy. All women testing negative for both cytology and hrHPV (PAP1, hrHPV negative) will be retested 18 months later (24 months after treatment). Only women testing negative at both 6 and 24 months will be referred to population-based screening. All other women need extra testing.

In our proposal, all women with histologically confirmed CIN2 or worse are treated, while those with low-grade disease (CIN 0 and 1) will be regularly tested (and could be treated if the low-grade lesion persists by moderate or severe dyskaryosis or persistent hrHPV infection).

CIN, Cervical Intraepithelial Neoplasia; hrHPV, high-risk type of the human papillomavirus; PBS, population-based screening; t, time in months after treatment

Table 6.2 Recommendations for women treated for high-grade cervical disease

- 1 HrHPV testing improves the sensitivity for detecting residual and recurrent (posttreatment) CIN2/3 and should therefore be included in the follow-up algorithm of treated women.
To detect posttreatment CIN2/3, hrHPV testing is more sensitive than cytology (relative sensitivity 1.15, 95%CI 1.06 – 1.25) with equal specificity (relative specificity 0.95, 95%CI 0.88-1.02). Hence, a positive hrHPV test may better identify women with an increased risk for progression to, and development of, posttreatment disease.¹¹
- 2 Follow-up of women treated for CIN2/3 should be done by cotesting (both cytology and hrHPV).
In the diagnostic setting the risk of missing residual or recurrent (posttreatment) CIN2/3 should be minimised as much as possible. The highest sensitivity (95%, 95%CI 91%–98%) of detecting posttreatment disease is reached by performing co-testing. As the a priori risk of these women is relatively high, the most optimal follow-up algorithm is the strategy that has the highest sensitivity.¹¹
- 3 Women treated for CIN2/3 with negative cotesting results after 6 months may omit the 12-month screening visit
Women testing negative for both cytology and hrHPV have a very low risk of developing posttreatment disease (overall CIN3+-risk of 1.4%). The CIN2+-risk after a single negative co-testing result (5-year CIN2+-risk of 3.0%, 95%CI 1.5%-6.1%) was similar to the risk after 3 consecutive negative cytologic test results (5-year CIN2+-risk of 2.9%, 95%CI 1.2%-7.1%).³
- 4 Women treated for CIN2/3 and having two negative cotesting results in the follow-up should be re-tested every 5 years.
Women who test negative for cotesting twice (at 6 and 24 months posttreatment) should be re-tested after 5 years, as their risk of developing CIN3+ in the next 5 years is minimal (0.0%, 95%CI 0.0%–3.0%).

CIN, Cervical Intraepithelial Neoplasia; hrHPV, high-risk type of the human papillomavirus; 95%CI, 95% confidence interval

Conclusion

The above-mentioned summary of our findings and the results of recent publications points to an urgent need to incorporate these results in new guidelines. We propose a new guideline consisting of combined testing with cytology and hrHPV at 6 and 24 months after treatment for CIN2/3 (Figure 6.1). By implementing these optimized guidelines with only 2 instead of 3 visits, we expect that the attendance rate will increase. As a result, detection of CIN2/3 lesions posttreatment will improve.

Although this article focuses on the Dutch situation, we feel that our proposed algorithm might also be implemented as preferred guideline in other countries with a population based screening program in place and which are able to perform hrHPV testing.

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